REMARKS

Status of the Claims

Claims 1 and 15, 16 and 18-33 are in the application.

Claims 1 and 15, 16 and 18-33 have been rejected.

Upon entry of this amendment, claims 1, 15, 16 and 18-33 will be pending.

Obviousness-type Double Patenting Rejections

Claims 1, 15, 16 and 18-33 have been rejected on the grounds of non-statutory, obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 7,045,286.

Applicants respectfully note that pending claims remain rejected on other grounds. Upon an indication of allowability of claims, Applicants shall promptly file a terminal disclaimer as appropriate.

Claims 1, 15, 16 and 18-33 have been provisionally rejected on the grounds of non-statutory, obviousness-type double patenting as being unpatentable over claims 1 2, 4 and 12 18 of co-pending application Serial No. 10/856,057.

Applicants respectfully note that this a provisional obviousness-type double patenting rejection because the conflicting claims have not yet been patented. If claims in co-pending application Serial No. 10/856,057 are indicated to be allowable and claims of the pending application are additionally indicated to be allowable, Applicants will promptly file a terminal disclaimer as appropriate. At this time, no terminal disclaimer is required.

Claims 1, 15-16 and 18-33 have been provisionally rejected on the grounds of non-statutory, obviousness-type double patenting as unpatentable over claims 1-4 of co-pending application Serial No. 10/333,542. Applicants respectfully note that this a provisional obviousness-type double patenting rejection because the conflicting claims have not yet been patented. If claims in co-pending application Serial No. 10/333,542 are indicated to be allowable

and claims of the pending application are additionally indicated to be allowable, Applicants will promptly file a terminal disclaimer as appropriate. At this time, no terminal disclaimer is required.

Applicants invite the Examiner to contact Applicant's undersigned representative at (610) 640-7855 should the Examiner deem claims, which are rejected on the grounds of non-statutory, obviousness-type double patenting, otherwise allowable. Applicants shall promptly prepare and file by telefax terminal disclaimer as appropriate.

Claim Rejection under 35 U.S.C. §103

Claims 1, 15, 16 and 18-33 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Kacian, et. al., (U.S. Pat. No. 5,888,729), in view of Eberwine et al. (U.S. Patent No. 5,922,553), Fields et al. (WO 94/26932) and Waggoner (U.S. Patent No. 5,627,027).

Kacian et. al. discloses a methods of detecting oligonucleotide sequences by extending a 3' portion of an oligonucleotide sequence by a primer/promoter, and subsequently amplifying RNA products through RNA polymerase which a identifies the newly extended promoter sequence. RNA amplification efficiency is optimized by use of a mixture of modified and unmodified primers.

Eberwine et al. discloses a method of immuno-aRNA using an RNA promoter on a cDNA sequence covalently coupled to an antibody which binds to a selected protein. Amplified RNA product is produced using radiolabeled nucleotides to produce a labeled amplified RNA product that has the radionucleotides incorporated within in by covalent bonds.

Waggoner discloses cyanine dye molecules that are specifically designed and intended to be used to covalently bond to molecules to be labeled such as fragments of DNA or RNA.

Fields et al. discloses a nucleic acid tagged immunoassay in which the oligonucleotide is attached to a ligand using a biotin streptavidin linker.

It is asserted that one of ordinary skill in the art would have been motivated to use the RNA-promoter driven cDNA as produced by the method of Kacian to couple onto an antibody because Eberwine taught coupling the RNA-promoter driven cDNA to an antibody. It is asserted

that one skilled in the art at the time of the invention was made would have been motivated to modify the method of Waggoner to stain the unlabeled RNA of Kacian for detecting and/or quantifying molecules expressing a selected epitope in a sample. It is asserted that one of ordinary skill in the art would have been motivated to apply the biotin-streptavidin as a linker for attaching the oligonucleotide to a monoclonal antibody taught by Fields. Applicants respectfully disagree.

Applicants respectfully assert that the combination of references does not produce the claimed invention. Applicants respectfully assert that the combination of references does not teach or suggest the claimed invention. Applicants respectfully assert that the combination of references teaches away from the claimed invention. One skilled in the art, viewing the references, would not be motivated to produce the claimed invention but instead would be taught to practice different subject matter than the claimed invention. One skilled in the art, viewing the references, would be motivated to practice subject matter that is explicitly contrary to the claimed invention as taught in the specification.

Kacian specifically discloses a way to detect RNA fragments amplified from a modified RNA promoter-driven target oligonucleotide. The specific purpose of Kacian is to modify a target oligonucleotide in solution to include a RNA promoter for more efficient amplification of RNA reaction products. Unlike the instant claims which use fluorescent stain to bind to amplified RNA products, Kacian uses probes labeled with acridinium-hydrogen peroxide to hybridize amplified RNA products.

Kacian discloses that a common method of detection and quantification of nucleic acid sequences is nucleic acid hybridization using a labeled probe which hybridizes to a target sequence (column 1 lines 52 to column 2 line 3). Kacian discloses numerous causes of short-comings in the sensitivity of assays based upon nucleic acid hybridization (column 2 lines 4-16). These short comings are overcome by amplification techniques (column 2 line 34 to column 3 line 34). Kacian discloses an amplification technique using nucleic acid sequences is nucleic acid hybridization using a labeled probe which hybridizes to a target sequence. Moreover, while Kacian generally refers to quantitation methods, no such methods are disclosed.

Eberwine et al. discloses a method which is "semi-quantitative" (see Eberwine column 2, line 34). Eberwine does not disclose a quantitative method in which the detectable signal is directly proportional to molecules expressing the selected epitope in the sample. Eberwine does not disclose unlabeled RNA amplification product. Eberwine does not disclose the use of fluorescent dye to stain the RNA amplification product.

In order to combine Kacian with Eberwine, one skilled in the art would have to modify Kacian as suggested in the Official Action to include an antibody linked to an RNA amplification template. Additionally, Kacian must be modified to eliminate the use of labeled nucleic acid probes to detect RNA amplification products that is taught by Kacian as well as the use of labeled nucleic acid bases in the preparation of RNA amplification product, and instead use with RNA staining of RNA amplification products as claimed in the instant application.

Waggoner specifically discloses cyanine dyes which are used to label, i.e., covalently bond to molecules sought to be detected (See Waggoner, column 2, lines 1-5; column 2, lines 25-32; column 2, lines 56-61; column 4, lines 35-42; column 7, lines 47-52; column 7, lines 61-65; column 8, lines 50-59; and column 9, lines 20-27). The specific purpose and intention of Waggoner is that the fluorescent label is covalently linked to the molecule to be detected. The invention in Waggoner is to provide the means to affect such covalent linkage. Waggoner expresses teaches away from non-unlabeled detection. Waggoner specifically teaches away from non-covalent use of the dyes. Waggoner does not disclose the use of fluorescent dye to stain unlabeled RNA. Waggoner does not disclose a quantitative method in which the detectable signal is directly proportional to molecules expressing the selected epitope in the sample.

Fields et al. does not make up for these deficiencies found in both Kacian, Eberwine and Waggoner. Fields et al. does not teach non-covalent use of the dyes. Fields et al. does not disclose the use of fluorescent dye to stain unlabeled RNA. Fields et al. does not disclose a quantitative method in which the detectable signal is directly proportional to molecules expressing the selected epitope in the sample.

The combination of Kacian, Eberwine, Waggoner and Fields does not establish a *prima facie* of obviousness. The combination of Kacian, Eberwine, Waggoner and Fields does not yield the claimed invention. For example, claim 1 requires the steps of

> (d) contacting the unlabeled amplified RNA product with a fluorescent dye which stains the unlabeled amplified RNA product.

Claims 23 contains essentially identical language. The combination of Kacian, Eberwine, Waggoner and Fields does not disclose staining the unlabeled amplified RNA product by contacting it with a fluorescent dye. The claims clearly refer to an element which is not present in the combination of prior art cited in the rejection. Accordingly, the combination does not establish a prima facie case of obviousness. It is well understood by those skilled in the art what is meant by staining with a dye. Those skilled in the art would readily recognize that none of the cited references teach or suggest

> contacting the unlabeled amplified RNA product with a fluorescent dye which stains the unlabeled amplified RNA product.

The references teach away for the combination and from the claimed invention. Kacian discloses the use of chemiluminescent labeled nucleic acid probes to hybridize to RNA amplification product. Eberwine et al. specifically teaches covalent linkage radiolabeled nucleotides within the amplified RNA product. Waggoner specifically discloses cyanine dyes which are used to covalently bond to molecules sought to be detected, not to stain nucleic acid molecules. In each case, the detectable moiety is covalently linked to a molecule which specifically binds to the molecule to be detected. In no case is the moiety a molecule such as a "dye" as set forth in claim 1 and 23. In no case "dye" as set forth in claim 1 and 23 contacted with the RNA amplification product to "stain" it as set forth in claim 1 and 23.

Those skilled in the art combining Eberwine et al., Waggoner and Fields et al. would neither be motivated nor conclude to stain an unlabeled RNA amplification product as set forth in the claims. Nothing in the combination of Kacian Eberwine et al., Waggoner and Fields et al. teach or suggest using a fluorescent dye to stain the RNA amplification product. To the contrary, Kacian teach detecting RNA amplification product using a labeled nucleic acid probe, and Eberwine et al. teaches detecting RNA amplification product by labeling the amplification product. Likewise, Waggoner specifically teaches away from non-covalent linkage.

Moreover, nothing in the combination of Kacian, Eberwine et al., Waggoner and Fields et al. teach or suggest a quantitative method in which the detectable fluorescent signal is used to

stain unlabeled amplification product such that the detectable fluorescent signal is directly proportional to molecules expressing the selected epitope in the sample Kacian refers to quantitation but provides no description of how such quantitation is specifically achieved. The combination of Kacian, Eberwine et al., Waggoner and Fields et al., neither teach nor suggest the claimed invention.

The claimed invention is not obvious in view of the combination of Kacian, Eberwine, Fields, and Waggoner. Applicants respectfully request that the rejection of claims 1, 15-16 and 18-33 under 35 U.S.C. §103(a) as being unpatentable over Kacian in view of Eberwine, Fields, and Waggoner be withdrawn.

Conclusion

Claims 1, 15, 16 and 18-33 are in condition for allowance. A notice of allowance is earnestly solicited.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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